REMARKS

I. Status of the Claims

Applicants thank the Examiner for entering the amendment submitted September 10, 2004. (Office Action at page 2.)

Applicants amend claim 8 to recite a "method of inhibiting angiogenesis or arteriogenesis in a patient in need thereof" rather than a "method of treating angiogenesis or arteriogenesis." Support for this amendment may be found in the application as a whole. Several dependent claims are amended to correspond to the amendment to claim 8 and to remove unnecessary words.

New claims 17-19 are also included in order to recite particular formulations of the claimed active antithrombin III. Those claims are also supported by the application as a whole, for example, at page 3, line 6, to page 4, line 7; page 8, lines 25-27; Figure 1; and the original claims.

II. The Claims are Definite under 35 U.S.C. §112, Second Paragraph

The Office rejects claim 8, contending that "active antithrombin III" is vague and indefinite and contends that the metes and bounds of that term are not defined in the specification. (Office Action at page 3.) However, the Office then goes on to cite the very definition of that term set forth at page 3 of the specification: "the active form of AT is defined by intact [ATIII] molecules with the ability to inhibit proteases such as thrombin and factor Xla, and by a strong interaction with heparin and related compounds." (Specification at page 3, lines 6-11.) These active antithrombin III proteins are further defined to include the alpha and beta isoforms. (*Id.* at page 3, lines 18-20; and see instant claim 9.)

Applicants note that a patent applicant may be his own lexicographer. Thus, a definition of a claim term set forth in the specification will apply when, as here, it is presented in sufficiently clear terms to one of ordinary skill in the art. See M.P.E.P. §2111.01(III). In this case, page 3 of the specification expressly "defines" the meaning of "active antithrombin III" based on a particular and readily measurable protease activity, ability to interact with heparin, an intact or full-length structure, and exemplary isoforms. That definition is sufficient notice to those of ordinary skill of the meaning of "active." Moreover, others in the art such as O'Reilly et al. also point out that the "active" form of antithrombin III is a "native intact form." (See US 2002/0076413 A1 at ¶ 0006; see also the discussion of O'Reilly et al.'s publication below.) Thus, the dictionary definition of "active" provided by the Office does not apply to the instant claims.

III. Claims 8-15 Are Novel over O'Reilly et al. in light of Webster's Dictionary

The Office rejects claims 8-15 as allegedly anticipated by O'Reilly et al. ("O'Reilly"; U.S. Publication No. 2002/0076413 A1) under 35 U.S.C. § 102(e). (Office Action at pages 3-4.) This rejection is also based upon the Office's interpretation of the meaning of "active antithrombin III," and the § 112, second paragraph, rejection that Applicants traverse above.

Applicants traverse this rejection. Moreover, Applicants have previously overcome the rejection in prior prosecution. (See Applicants' remarks filed on June 10, 2004, and the subsequent Office Action of June 24, 2004.) In light of that fact, and the remarks that follow, Applicants request the withdrawal of this rejection.

In order to anticipate a claim, a single publication must teach, either expressly or inherently, each and every element of the claim, in as complete detail as contained

within the claim. M.P.E.P. § 2131; *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Richardson v. Suzuki Motor Co.*, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989). O'Reilly cannot anticipate any of claims 8-15 because it does not teach or suggest administering "active antithrombin III."

Instead, O'Reilly specifically points out that "active" antithrombin III is the "native, intact form." O'Reilly does not administer that form, but instead administers a cleaved form called "R-AT3." (See O'Reilly at ¶¶ 0007, 0041, 0090, and Figure 1.) O'Reilly also mentions another purified form called "L-AT3." (O'Reilly at ¶¶ 0042 and 0090, and Figure 1.) That form is also not an "active antithrombin III" as Applicants claim, but is "no longer active as a serine protease inhibitor." In contrast, the instant specification requires the claimed and administered "active antithrombin III" to have serine protease activity. (Page 3, lines 6-11.) Moreover, Applicants' specification expressly states that O'Reilly's forms are distinct from the claimed "active" form. (Specification at page 2, lines 29-33.)

IV. Claims 8-10, 13, and 15 are Novel over Romisch et al. in light of Webster's Dictionary

Next, the Office contends that claims 8-10, 13, and 15, are inherently anticipated by a patent to Romisch et al. ("Romisch"; U.S. Patent No. 6,399,572 B1), which the Office interprets in light of Webster's Dictionary, as discussed above. (Office Action at pages 4-5.) Applicants traverse this rejection.

First, this rejection is based upon the Office's interpretation of "active," which does not take into account the definition of "active antithrombin III" provided in Applicants' specification.

A novelty rejection based upon inherency requires a finding that the allegedly inherent result or characteristic necessarily flows from the prior art teachings. (M.P.E.P. § 2112(IV) (emphasis in original).) In contrast, the Office here merely asserts that Romisch's method would anticipate because it generally uses ATIII to treat sepsis, vasculitis and rheumatoid arthritis. (Office Action at page 5.) For example, Romisch points out also that "the anti-inflammatory properties of AT III concentrates [sic] are distinct from its anti-thrombin and anti-clotting capability." (Romisch at col. 1, lines 56-58.) Thus, one of ordinary skill in the art reviewing Romisch's disclosure would not conclude that the use of antithrombin III to reduce inflammation caused by lipopolysaccharides, for example, would necessarily, always result in inhibition of angiogenesis or arteriogenesis. (See, for example, Romisch at Tables 1-3.)

Further, a *prima facie* case of anticipation requires substantial evidence or scientific reasoning firmly grounded in fact. M.P.E.P. § 2112(V); *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); *In re Zurko*, 59 U.S.P.Q.2d 1693 (Fed. Cir. 2001). Applicants submit that the Office has not set forth a *prima facie* case here because it has not demonstrated how the control of lipopolysaccharide-induced cytokines would necessarily inhibit angiogenesis or arteriogenesis. Thus, Applicants request the withdrawal of this rejection.

V. Claims 8-15 are Novel over Green et al. in light of Webster's Dictionary

The Office also contends that claims 8-15 are anticipated by a patent to Green et al. ("Green"; U.S. Patent 6,593,291 B1). Applicants traverse this rejection as well.

As with other rejections herein, this rejection is based upon the Office's interpretation of "active," which does not take into account the definition of "active

antithrombin III" provided in Applicants' specification. Applicants' specification defines the antithrombin III to be administered as meeting several distinct criteria such as an "intact" state as well as "ability to inhibit proteases such as thrombin and factor XIa" and "strong interaction with heparin and related compounds." (Specification at page 3, lines 6-15.)

Green does not anticipate the instant claims because one of ordinary skill in the art could not "at once envisage" the "active antithrombin III" recited in claim 8 and its dependents from the disclosure of Green. See M.P.E.P. § 2131.02; *Ex parte A*, 17 U.S.P.Q.2d 1716 (Bd. Pat. App. & Inter. 1990). For example, that claimed antithrombin III meets the definition of the instant specification described above, and may be an alpha or beta isoform, or a mixture of the two, according to claim 9. Claims 17-19 impose further restrictions.

In contrast, Green discloses a vast array of compositions including, apparently, every protein involved in the blood coagulation pathway and every protein that binds or affects the activity of tissue factor, and peptide fragments derived from that multitude of proteins. Green also does not specify any particular isoforms or mixtures of isoforms for any of the proteins. Green's list thus comprises tens to hundreds of different proteins and their associated protein fragments. (See, for instance, Green at col. 4, lines 26-46; at col. 6, line 31, to col. 7, line 10; and at col. 10, lines 6-59.) Further, Green's teachings do not point to using active (and thus intact) antithrombin III, including the alpha and/or beta isoform as the present inventors claim. For example, Green's example 4 at column 18 uses a cleaved form of antithrombin III in which cleavage was

induced by complexing with factor Xa. (Green at col. 18, lines 37-48.) The example further explains that this cleavage event enhanced the activity of antithrombin III. (*Id.*)

Thus, Applicants request the withdrawal of this rejection.

VI. Claims 8-10, 13, and 15 are Novel over Emerson in light of Webster's Dictionary

The Office also contends that claims 8-10, 13, and 15 are anticipated by Emerson (*Blood Coag. Fibrinolysis* 5(1): S 37-45). Applicants also traverse this rejection and request its withdrawal.

This rejection is also based upon the Office's interpretation of "active," which does not take into account the definition of "active antithrombin III" provided in Applicants' specification. Like Green, Emerson does not discuss whether the antithromin III used in the work was intact or whether any particular type of isoform or mixture of isoforms was used.

The Office asserts that Emerson anticipates those claims because it allegedly "practices the steps of the instantly claimed method, namely, that an infectious disease was treated by the administration of AT3." However, as Applicants explained above in discussing the rejection over Romisch, antithrombin III is known in the art to have a variety of actions including an anti-inflammatory action. Hence, use of antithrombin III as an anti-inflammatory agent does not necessarily mean that the same administration of antithrombin III will also necessarily inhibit angiogenesis or arteriogenesis. Furthermore, Emerson does not allow one of ordinary skill in the art to envisage treatment with the active, and thus intact, antithrombin III in the alpha or beta isoform, or a mixture thereof as recited in instant claim 8 or claim 9 or in any of claims 17-19. (See

Emerson at S 38, col. 1, under "materials and methods." Therefore, Emerson cannot inherently anticipate any of the instant claims.

VII. Claims 8, 10, and 16 are Non-obvious over O'Reilly in view of Antunes et al. and Webster's Dictionary (1994)

The Office contends that claims 8, 10, and 16 are obvious over O'Reilly, in combination with Antunes and Webster's Dictionary. This combination fails to render those claims obvious.

There are three distinct requirements for a *prima facie* case of obviousness. First, the references must teach or suggest every claim element. M.P.E.P. §§ 2142 and 2143.03. As described in a previous section of this Reply, O'Reilly fails this test because it does not suggest using "active antithrombin III" in as Applicants have defined that term. As discussed above, the dictionary definition of "active" that the Office cites does not apply here because Applicants have provided a specific definition of "active antithrombin III" in the instant specification. Moreover, O'Reilly does not teach the alpha and beta isoforms of antithrombin III or mixtures thereof.

Second, for a *prima facie* case of obviousness, there must be a motivation to modify the teachings of the cited references. M.P.E.P. §§ 2143 and 2143.01. That motivation must come from the references themselves or from the knowledge generally available to one of ordinary skill in the art; not from the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. § 2142. Further, the mere fact that the references *can* be combined or modified does not itself render the combination obvious. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The modification or

combination must be *desirable*, not merely feasible. M.P.E.P. § 2143.01; *Winner v. Wang*, 53 U.S.P.Q.2d 1580, 1587-8 (Fed. Cir. 2000).

This combination also fails this test. In fact, O'Reilly as a whole teaches away from Applicants' claims because it repeatedly concludes that the S-AT3 "active" form is not useful in combating angiogenesis. Courts have long pointed out that teaching away is "strong evidence of unobviousness." *See, e.g., In re Hedges*, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986).

Third, a *prima facie* case of obviousness requires a reasonable expectation of success in performing the combined teachings, based on those teachings themselves or the prior art. M.P.E.P. § 2142. This combination likewise fails this test because O'Reilly strongly teaches away from using any "active" antithrombin III form, as noted above. Based on O'Reilly's results, one would not expect that the intact, active form that Applicants use to successfully affect angiogenesis or arteriogenesis.

Antunes does not bridge this large gap in O'Reilly's teachings because it does not discuss antithrombin III.

For all of the above reasons, Applicants request the withdrawal of this rejection.

VIII. Claims 8, 10, and 16 are Non-obvious over Green in view of Antunes et al. and Webster's Dictionary (1994)

Finally, the Office contends that claims 8, 10, and 16 are obvious over Green, in combination with Antunes and Webster's Dictionary. Applicants traverse this rejection for the same reasons that Applicants traverse the rejection over the combination involving O'Reilly.

Like O'Reilly, Green also teaches away from the "active antithrombin III" of instant claim 8 because it teaches that cleaved antithrombin III should be used. For instance, in Green's example 4 at column 18, Green states that "it is likely that complexing with factor Xa and/or proteolytic cleavage of [a] limited number of residues of AT3 may enhance the anti-angiogenic activity of AT3." (Green at col. 18, lines 46-49.) Thus, there is no motivation in Green for one of ordinary skill in the art to use an active, intact form of antithrombin III as claimed here. Antunes does not bridge this large gap in Green's teachings because it does not even discuss antithrombin III.

Therefore, Green and Antunes, in further view of Webster's Dictionary, do not teach all of the elements of claim 8 and do not provide motivation to combine the elements they do teach in such a way that would render claim 8 obvious. Thus, Applicants request the withdrawal of this rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any required fees not found herewith to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: April 29, 2005

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